



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,620	12/30/2003	Xiaobing Wu	04577/0200726-US0	6175

7278 7590 07/26/2006

DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

EXAMINER

SAJJADI, FEREDOUN GHOTB

ART UNIT	PAPER NUMBER
----------	--------------

1633

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/750,620	Applicant(s) WU ET AL.	
	Examiner Fereydoun G. Sajjadi	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) 12-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5.4.2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response of May 4, 2006, to the non-final action dated January 4, 2006 has been entered. Claims 2, 3, 9 and 11 were amended and claim 18 was newly added by the Applicant in the paper dated May 4, 2006. Claims 12-17 remain withdrawn without traverse, and claims 1-11 and 18 are currently under examination.

Response to Claim Objections – Duplicate Claims

Claim 4, stands objected to, as being a substantial duplicate of claim 3. The objection set forth on p. 2 of the previous office action dated January 4, 2006 is maintained for claim 4 for reasons of record. In view of Applicant's arguments, the objection to claims 6 and 7 is hereby withdrawn.

Applicant's arguments with regards to claim 4 have been fully considered, but not found to be persuasive. Applicant disagrees with the finding that claim 4 is a substantial duplicate of claim 3, arguing that claim 3 recites any AAV vector cell strain wherein the cell is a BHK-21 cell, whereas claim 4 sets forth the specific cell strain BHK/HO-1.

Such is not the case. Claim 3 is directed to the AAV vector cell strain of claim 2. The AAV vector cell strain of claim 2 comprises the HO-1 gene of claim 1. Thus, the transformation of a BHK-21 cell with said vector comprising the HO-1 gene, as recited in claim 3 would result in the cell strain BHK/HO-1, i.e. the cell strain of claim 4. The instant specification does not define a specific BHK/HO-1 cell strain, but states: "The cells transfected with recombinant plasmid vector pSNAV1/HO-1 can be selected for bearing the neo^r gene, which can be used to produce rAAV/HO-1 and designated as BHK/HO-1." (p. 10).

Hence, the objection is maintained for reasons of record and expanded upon by the commentary given above.

Response to Claim Rejections - 35 USC § 112-Biological Deposit

Claims 1-10 were previously rejected under 35 USC § 112 first paragraph, as lacking an enablement without either complete evidence that the plasmid pSNAV1/HO and the recombinant

Art Unit: 1633

virus HSV1-rc, recited in the claims are known and readily available to the public or complete evidence of the deposit of the biological material, in the first office action dated January 4, 2006.

In view of submitted Exhibits A and B, specifically teaching the construction of HSVI-rc and pSNAV1, together with Applicants arguments, this rejection is hereby withdrawn.

New Claim Rejections - 35 USC § 112-Indefinite

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the removal of the *in situ* perfused organ from the animal in which it was perfused prior to transplant in another animal. Claim 11 recites administering directly to the organ by *in situ* perfusion an effective amount of a recombinant adeno-associated viral vector comprising the HO-1 gene to increase HO-1 gene expression in the an animal transplanted with the perfused organ. Thus it is not clear how said administering may result in HO-1 gene expression in the transplanted animal when the perfused organ remains *in situ* in the donor animal.

Response to Claim Rejections - 35 USC § 112-Indefinite

Claim 11 was rejected under 35 USC § 112 second paragraph, as being unclear, in the first office action dated January 4, 2006.

In view of Applicant's amendment to the claim, this rejection is hereby withdrawn, but the claim remains rejected for reasons set forth above.

Claim Rejections - 35 USC § 112-Lack of Enablement

Claim 11 stands rejected in modified form, and claim 18 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a method of providing for increasing expression of an HO-1 gene in any organ of an animal, wherein the method comprises administering directly to the organ by *in situ* perfusion an effective amount of a recombinant adeno-associated viral vector comprising the HO-1 gene.

This rejection is based on the absence of an enabling disclosure for a method of increasing HO-1 gene expression in any organ of an animal by directly administering an AAV vector comprising the HO-1 gene to said organ by *in situ* perfusion. The lack of an enabling disclosure was identified by the Office after analysis of the disclosure provided in the instant application. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

Claim 11 encompasses the administration of a recombinant AAV virus comprising an HO-1 gene to any organ of an animal by *in situ* perfusion, for gene therapy.

The specification discloses stable expression of HO-1 following delivery of 1×10^{12} vector genomes in rat heart grafts (Example 1, p.13). The grafts are described as allogeneic heart transplants perfused *in situ* by administering rAAV/HO-1 vector into the rat heart graft via the coronary artery. The grafts were then preserved in cold HTK solution for 6 hours before transplant (p. 10). The specification further discloses that expression of the HO-1 gene was detectable in endothelial cells and cardiomyocytes, but was only detectable in cardiomyocytes after 30 days. However, the specification provides no additional examples of transplanting other organs (such as the brain) by the *in situ* AAV perfusion method and cold storage prior to transplantation. The prior art is silent on the *in situ* perfusion of AAV vector, and subsequent transplant of any organ to increase the expression of a target gene. Clearly, not any organ of an animal that would include the brain, would be amenable to the *in situ* perfusion and cold storage prior to transplantation, as claimed.

The prior art of Li et al. (Gene Therapy 10:1807-1813; 2003) describe AAV vector mediated intracardiac gene transfer by perfusion of hamster heart (Abstract). Li et al. also note the lack of gene expression in the blood vessels of the AAV vector treated heart, despite expression in the cardiomyocytes, thereby implicating partial therapeutic efficacy, that may require a combination of gene therapy and drug therapy (last paragraph, p. 1811).

With regard to gene delivery for therapy, Thomas et al. (Nature Rev./Genet. 4: 346-358; 2003) state: "The science of gene therapy has a turbulent history. Initially perceived as a revolutionary new technology with the promise to cure almost any disease-provided that we understand its genetic or molecular basis-enthusiasm rapidly waned as clinical trial after clinical trial failed to show efficacy. The stumbling block seemed to be the vehicles that were used to deliver the therapeutic genes to the target tissue; early recombinant viral vectors were inefficient, failed to persist in host cells and transgene expression was typically short lived. Then, in 1999, an adverse patient reaction to an adenovirus vector during a clinical safety trial led to the realization that the failure to understand the biology of vector interactions with the human immune system could have fatal consequences. The year 2000 brought the first gene-therapy

Art Unit: 1633

success in which three children were cured of a fatal immunodeficiency disorder, but this therapy has subsequently caused a leukemia-like disease in 2 of the 11 patients who have been treated” (column 1, p. 346). Thomas et al. further state: “The ability to accurately predict vector-related side effects at a particular dose is confounded in human studies by the degree of variability between immune responses in different individuals”. ...“T-cell responses can still be elicited against the expressed transgene product, particularly if the vectors transduce cells that are robust for antigen presentation, including dendritic cells. The route of vector administration might affect the degree to which dendritic cells are transduced; route of administration has a profound effect on the development of T-cell responses to transgenes that are expressed from AAV vectors. Pre-existing humoral immunity to the parental wild-type viruses is another obstacle that affects all classes of viral vector.” (column 2, p. 353, last two paragraphs). Thus, the art at the time of filing clearly establishes that gene therapy using AAV vectors as well as its application to *in situ* heart perfusion remains unpredictable.

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. At the time of the instant invention, the skilled artisan not have been able to predict without undue experimentation that the AAV mediated transfer of the HO-1 gene to any *in situ* perfused organ of an animal would result in increased HO-1 gene expression in said organ following its transplantation and provide a therapeutic benefit.

Therefore, in view of the art recognized high level of unpredictability in AAV mediated gene therapy, especially in combination with *in situ* organ perfusion and subsequent transplantation, and the lack of guidance provided by the specification for the same, and the breadth of the claims, it would have required undue experimentation for one of skill in the art to perform the methods of the claims. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Response to Claim Rejections - 35 USC § 112-Lack of Enablement

Art Unit: 1633

Claim 11 was previously rejected under 35 USC § 112 first paragraph, in the first office action dated January 4, 2006, as not enabled. Applicants have amended claim 11 to recite “increasing the expression of HO-1 gene in an organ of an animal, wherein the method comprises administering directly to the organ by *in situ* perfusion. Applicant argues that the Examiner’s reliance on two articles (Verma and Pfeifer) to support the contention that the state of the prior art suggests “vector targeting *in vivo* to be unpredictable and inefficient” is inapplicable to the presently claimed invention, because the Verma article was published 6 years prior to the filing of the instant application and that neither Verma nor Pfeifer disclosed or suggested the directed delivery to the organ or interest using *in situ* perfusion.

Applicant’s arguments have been fully considered but not found to be persuasive. The Verma and Pfeifer references provided information relating to the general problems and unpredictability of gene therapy protocols using viral vectors. These issues as well as the subject of *in situ* organ perfusion are addressed and expanded upon in the foregoing rejection, above.

Hence, the rejection is maintained for reasons of record and expanded upon by the commentary given above.

Claim 9 was previously rejected under 35 USC § 112 first paragraph, in the first office action dated January 4, 2006, as not enabled. In view of Applicant’s amendment of the claim to specify the production of rAAV/HO-1 *in vitro*, and Applicant’s arguments, this rejection is hereby withdrawn.

Response to Claim Rejections - 35 USC § 102

Claims 1-10 were previously rejected under 35 USC § 102(a) as anticipated by Tsui et al. in the first office action dated January 4, 2006. In view of the 37 CFR § 1.132 declaration by the inventors, declaring under penalty of perjury, that the additional authors of Tsui et al. did not participate in the conception of the instant invention, Tsui et al. no longer qualifies as a 102(a) anticipatory reference. Thus, the rejection is hereby withdrawn.

Claims 1, 5-8 and 11 were previously rejected under 35 USC § 102(b) as anticipated by Dzau et al. in the office action of January 4, 2006. Applicant correctly notes that Dzau does not

Art Unit: 1633

qualify as a 35 USC § 102 (b) reference. Further, in view of Applicant's arguments, the claim rejections are hereby withdrawn.

Claims 2 and 3 were previously rejected under 35 USC § 102(a) as anticipated by Coffin et al. in the office action of January 4, 2006. Applicant correctly notes that Coffin is misclassified as a 35 USC § 102 (a) reference. Further, in view of Applicant's arguments, the claim rejections are hereby withdrawn.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 are newly rejected under 35 USC 103(a) as being unpatentable over Coffin et al. (U.S. Patent Application Publication 2005/0226847, filed Apr. 11, 2003), in view of Wilson et al. (U.S. Patent 6,261,551; Patented July 17, 2001), and further in view of Dzau et al. (U.S. Patent Application Publication 2003/0022870, filed Jun. 3, 2002).

The claims 1-10 embrace a recombinant plasmid vector pSNAV/HO-1, comprising an HO-1 gene, said gene under the control of the CMV promoter and flanked by ITR sequences; an AAV cell strain BHK/HO-1; recombinant virus produced from said cell strain and a process for production of rAAV/HO-1 virus, comprising transfecting said cell strain with recombinant HSV virus.

Coffin et al. discuss the construction of an adeno-associated virus producer system, using a recombinant HSV virus (Abstract). The HSV virus of Coffin et al. serves as a helper virus for production of AAV, "having improved properties compared to previous herpes helper viruses"

Art Unit: 1633

(paragraph [0006], column 1, p. 1). The HSV virus of Coffin et al. “comprises AAV rep and/or cap genes and/or AAV vector sequence” (paragraph [0017], column 2, p. 1), and may be used in an AAV producer line that supports the growth of the herpes virus. “A particularly preferred cell line is based on BHK or Vero cells” (paragraph [0080], column 1, p. 5), with the BHK cells providing greater yields of AAV (paragraph [0132], p. 7). Additionally described is an AAV construct containing AAV ITRs flanking a CMV GFP-bGH poly A cassette (Example I, p. 6). However, the CMV GFP-bGH poly A cassette must be introduced into a plasmid shuttle vector for propagation and further introduced into a cell for packaging and virus production (paragraph 0099], p. 6).

Wilson et al. teach the production of AAV vectors comprising a selected transgene under the control of regulatory sequences (Abstract). Specifically described is the preparation of recombinant AAV vectors and plasmid derived sequences carrying ITRs and the CMV early promoter (column 20), in addition to plasmids encoding both the AMP resistance gene and the neo resistance gene under the control of the SV40 promoter (Fig. 1). Therefore, the use of plasmid vectors containing the Amp, SV40 and Neo regions for construction of AAV vector is specifically taught by Wilson et al.

While neither Wilson et al., nor Coffin et. al. describe the use of the HO-1 gene in their AAV production and delivery system, Coffin et al. state: “An AAV vector of the invention may be formulated with a pharmaceutically acceptable carrier or diluent and/or may be administered to a patient in a method of treatment of a disease or disorder, for example by gene therapy”, thus providing the motivation to include any therapeutically effective gene, including the HO-1 gene in the AAV vector and enable the efficient transfer of nucleic acid encoding HO-1 gene to cells or tissues of interest.

Dzau et al. describe methods of utilizing recombinant AAV vectors expressing human heme oxygenase 1 (hHO-1) cDNA under the transcriptional control of the human cytomegalovirus (CMV) early gene promoter, rAAV/CMV-hHO-1, having AAV inverted terminal repeats (ITR) encoding replication and packaging signals and the BGH-pA providing the polyadenylation signal for the HO-1 gene (paragraph [0022], column 2, p. 2 and Fig. 1A). Dzau et al. further describe rAAV, carrying the HO-1 gene, administered as “a vector for directed delivery of the cytoprotective gene HO-1 into the rat myocardium. A single delivery of

Art Unit: 1633

an AAV/HO-1 composition was found to reduce myocardial injury”. “AAV-mediated transfer of the hHO-1 gene led to a dramatic reduction (>75%) in left ventricular myocardial infarction” (paragraphs [0017 and 0018], column 1, p. 9) “hHO-1 gene expression in left ventricle eight weeks after rAAV-mediated intramyocardial gene transfer” (paragraph [0024], column 2, p. 2 and Fig. 1C).

Thus, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the AAV vector of Dzau et al. containing the HO-1 gene under the control of a CMV promoter sequence, in a process to produce recombinant AAV/HO-1 virus, using the recombinant HSV helper virus and BHK cell of Coffin, that would require the cloning of the HO-1 expression cassette in a plasmid vector containing the Amp and SV40-neo regions, as taught by Wilson et al., resulting in the practice of the instantly claimed invention. It would have been obvious to combine the AAV/HO-1 vector of Dzau et al. and the virus production system of Coffin et al. and Wilson et al., because the combination would result in improvements in virus packaging and virus production. The state of the art at the time of the invention had demonstrated the routine methods for construction of plasmid vectors containing selectable markers, containing AAV sequences. Therefore, an artisan of skill, having combined the elements of HSV helper virus containing the AAV rep and cap genes, the BHK cell line and an AAV vector capable of expressing the HO-1 gene, would have a reasonable expectation of success in producing rAAV/HO-1 virus in BHK cells.

Response to Claim Rejections - 35 USC § 103

Claims 1-10 were rejected under 35 USC 103(a) as being unpatentable over Coffin et al. in view of Dzau et al., in the first office action dated January 4, 2006. Applicant has traversed the rejection, arguing that neither Dzau nor Coffin disclose the elements of Amp, SV40 and Neo region. In view of the deficiency, this rejection is hereby withdrawn.

Conclusion

No claims are allowable.

Art Unit: 1633

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(703) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633



ANNE M. WEHBE PH.D
PRIMARY EXAMINER

